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Green tea consumption, genetic susceptibility, PAH-rich smoky coal, and the risk of lung cancer

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Abstract

Experimental evidence suggests that green tea (*Camellia sinesis*) may reduce the risk of lung cancer through several hypothesized mechanisms including scavenging oxidative radicals, inhibition of tumor initiation, and modulation of detoxification enzymes. However, epidemiologic results have not been consistent as to the relationship between green tea consumption and lung caner prevention. We employed a population-based case-control study of 122 cases and 122 controls to investigate the effect that green tea consumption may have on the risk of lung cancer and whether polymorphisms in 8-oxoguanine-DNA glycosylase (*OGG1*), glutathione-*S*-transferase M1 (*GSTM1*), and aldo-keto reductase 1C3 (*AKR1C3*) modify such an association. Daily green tea consumption was associated with a non-significant reduction in lung cancer risk. However, the effect of smoky coal exposure was higher for non-drinkers (odds ratio (OR) = 4.93; 95% confidence interval (95% CI) = 1.27–19.13) than for drinkers (OR = 1.88; 95% CI = 1.01–3.48). Further, among individuals with the *OGG1* Cys^{326} allele, daily consumption was associated with a 72% reduction (95% CI = 0.09–0.94). Among *GSTM1* null homozygotes, those who consumed green tea daily had a non-significant reduction in risk compared with non-consumers. Green tea consumption had no effect among *OGG1* Ser^{326} homozygotes or *GSTM1* carriers. In addition, *AKR1C3* genotype did not modulate the effect of green tea consumption. The chemopreventive effects of green tea in this population may be restricted to individuals who are particularly susceptible to oxidative stress and oxidative DNA damage.

Keywords: Green tea; Smoky coal; Lung cancer; *OGG1*; *AKR1C3*; *GSTM1*

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1. Introduction

Green tea, derived from *Camellia sinesis*, has been hypothesized widely to be a chemopreventive agent that may reduce the risk of cancer, including lung cancer. Compelling evidence from in vitro and animal assays indicates that polyphenols, generally thought to be the active ingredient in green tea, reduce tumor formation, tumor size, and cellular proliferation [1–8]. Green tea may protect through several hypothesized mechanisms including scavenging reactive oxygen species (ROS), inhibition of tumor initiation, and modulation of detoxification enzymes [8]. However, epidemiologic data have yet to convincingly demonstrate that green tea consumption reduces the risk of lung cancer. While several epidemiologic studies have shown green tea consumption to be associated with a reduction in lung cancer risk [9–11], others have shown no effect [12–14], and one study has shown an increase in risk [15].

Residents of Xuan Wei, China, regularly consume green tea and are exposed to high concentrations of PAHs from the combustion of smoky coal used in home heating and cooking [16–20]. We have previously shown that exposure to PAHs from smoky coal in this population was associated with lung cancer (odds ratio (OR) = 2.4; 95% confidence interval (95% CI) = 1.3–4.4) [18]. In addition to forming bulky PAH–DNA adducts, PAHs can be metabolized by dihydrodiol dehydrogenases, members of the aldo-keto reductase (AKR) superfamily, which form ROS that can lead to 8-hydroxyguanine (8-OH-G) DNA damage [21–23]. Further, auto-oxidation of PAH-derived intermediate catechols and subsequent redox cycling of quinones can generate ROS that cause oxidative DNA damage [23–25].

Genetic polymorphisms in aldo-keto reductase 1C3 (*AKR1C3*), 8-oxoguanine-DNA glycosylase (*OGG1*), and glutathione-*S*-transferase M1 (*GSTM1*) may influence oxidative DNA damage and ultimately carcinogenesis. *OGG1* codes for a DNA glycosylase involved in base excision repair of 8-OH-G that arises from ROS [26,27]. *GSTM1* is a phase II enzyme that is important in quenching and detoxifying ROS and their derivatives [28]. We have previously reported that individuals with at least one *OGG1* Cys^{326} allele had an odds ratios of 1.9 (95% CI = 1.1–3.3) compared with *OGG1* Ser^{326} homozygotes and that *AKR1C3* Gln^{5} allele carriers were at increased risk of lung cancer (OR = 1.8; 95% CI = 1.0–3.5) [29]. Further, we have also shown that *GSTM1* null homozygocity was associated with an odds ratio of 2.3 (95% CI = 1.3–4.2) compared with *GSTM1* carriers in this population [18].

Considering that green tea polyphenols are potent antioxidants and that genetic polymorphisms in *AKR1C3*, *OGG1*, and *GSTM1* may play important roles in mitigating oxidative DNA damage, the population in Xuan Wei provided a unique opportunity to study the potential chemopreventive effects of green tea use and the pathogenesis of PAH-induced lung cancer. We report herein on a study to investigate the potential effect that green tea consumption may have on lung cancer risk and whether *AKR1C3*, *OGG1*, and *GSTM1* modify the effect of green tea use on lung cancer risk. Specifically, we examined green tea consumption stratified by genetic polymorphisms in *AKR1C3*, *OGG1* and *GSTM1* that may increase susceptibility to DNA damage from ROS and lung cancer.

2. Materials and methods

This population-based case-control study has been described elsewhere [18,29]. Briefly, cases and controls were recruited into the study over a 1-year period between March 1995 and March 1996. In total, 122 primary, incident cases of lung cancer and 122 controls were enrolled matched on age (±2 years), gender, village of residence, and type of fuel currently used for cooking and home heating. The control/case-matching ratio was 1:1. Information was collected from in-person interviews regarding demographic data, smoking history, family medical history, smoky coal use, and green tea consumption. Participants were asked how often they drank green tea: never, sometimes (two to three times per week), or often (at least once per day). One control was missing green tea use and was excluded from the analysis. To estimate cumulative lifetime coal use, each participant was queried about the number of tractor loads of coal that were purchased from the local coal distributor.

Genotype analyses were previously described [18,29]. DNA was available for 122 cases and controls for the *GSTM1* genotype; only 118 cases and 109 controls were available for *OGG1* and *AKR1C3*. For human

subject protection, this study was conducted according to the recommendations of the World Medical Association Declaration of Helsinki. The research protocol was approved by a US EPA Human Subjects Research Review Official for international research projects, and informed consent was obtained from all subjects in this study.

Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals for the main effects between green tea use and lung cancer. However, matching between cases and controls was not retained for the genotype analyses because some matched case-control pairs were missing genotype data. For these analyses, unconditional logistic regression was used to calculate OR and 95% CI. The unconditional logistic models were initially adjusted for age, gender, pack-years of smoking, and smoky coal exposure. The most parsimonious model was determined by removing variables that did not alter the point estimate by more than 10%; the final models included only age and gender. Participants were stratified by these genotypes to examine the potential effect modification on green tea consumption and lung cancer. *OGG1* Ser/Cys^{326} heterozygotes and Cys/Cys^{326} homozygotes were combined because of the low proportion of Cys^{326} homozygotes. Similarly, *AKR1C3* His^{5} homozygotes and *AKR1C3* His/Gln^{5} heterozygotes were combined because of the low proportion of *AKR1C3* His^{5} homozygotes. For *GSTM1*, homozygotes for *GSTM1* present and heterozygotes (i.e., individuals with one *GSTM1*

Table 1
Selected characteristics of lung cancer cases and controls in Xuan Wei, China

	Cases ($n = 122$)	Controls ($n = 121$)	p-Value
Sex			
Male	79 (64%)	78 (65%)	
Female	43 (36%)	43 (35%)	0.96[a]
	Mean (S.D.)		p-Value
Age (years)	54.71 (11.45)	54.44 (11.97)	0.86[b]
Smoky coal (lifetime tonnes)	172.02 (105.58)	129.42 (76.81)	<0.001[b]
Smoking (pack-years)[c]	27.59 (20.13)	25.04 (21.45)	0.44[b]
	Number (%)		OR (95% CI)
Smoky coal use[d]			
<130 tonnes	51 (42%)	58 (48%)	1.0
≥130 tonnes	71 (58%)	64 (52%)	2.4 (1.3–4.4)
GSTM1[d]			
Carrier	40 (33%)	62 (51%)	1.0
Null	82 (67%)	60 (49%)	2.3 (1.3–4.2)
OGG1[e]			
Ser/Ser	37 (31%)	51 (47%)	1.0
Ser/Cys + Cys/Cys	81 (69%)	58 (53%)	1.9 (1.1–3.3)
AKR1C3[e]			
His/His + His/Gln	22 (19%)	33 (29%)	1.0
Gln/Gln	94 (81%)	79 (71%)	1.8 (1.0–3.5)
Green tea use			
Never	27 (22%)	23 (19%)	1.0
2–3 times per week	28 (23%)	26 (21%)	0.84 (0.38–1.85)[f]
≥1 per day	67 (55%)	72 (60%)	0.59 (0.26–1.37)[f]
p for trend			0.20

[a] p based on χ^2-test.
[b] p based on t-test.
[c] Males only.
[d] Results previously published in Lan et al. [18].
[e] Results previously published in Lan et al. [29].
[f] Conditional logistic regression matched on age, gender, village of residence, type of heating, and cooking fuel currently used and further adjusted for pack-years of smoking.

present and one deleted allele) were defined as *GSTM1* carriers. The *p* for trend statistics was determined by the *p*-value for the coefficient of the green tea use as a continuous variable, while adjusting for covariates. *p* for interaction was determined with unconditional logistic regression by the *p*-value of the coefficient for the product term of green tea use and genotype while adjusting for covariates.

3. Results

Males (82%) were much more likely to regularly drink green tea than were females (21%). Similarly, 93% of males were smokers while only one female smoked. Cases and controls were comparable on other factors (Table 1). Lifetime smoky coal use ≥130 tonnes, *GSTM1* null genotype, *OGG1* Cys^{326} allele, and *AKR1C3* Gln^{5} allele have previously been reported to be associated with the risk of lung cancer [18,29]. Daily green tea consumption was associated with reduced risk of lung cancer (OR = 0.59; 95% CI = 0.26–1.37), although the confidence intervals included the null. Since the prevalence of green tea use was substantially higher among male study participants, we analyzed the effects of daily green tea consumption separately for males (OR = 0.63; 95% CI = 0.17–2.23) and females (OR = 0.70; 95% CI = 0.22–2.23); the *p* for interaction was not significant (*p* interaction = 0.88). In addition to the higher prevalence of green tea use, smoking was also more prevalent among males. To further control for this difference, we restricted the analysis to male smokers and found no indication that smoking altered the effect of daily green tea use (OR = 0.72; 95% CI = 0.15–3.40).

Because smoky coal exposure has been shown to be associated with lung cancer in this population, we examined the effect of green tea consumption separately for those using <130 tonnes and those using ≥130 tonnes of lifetime smoky coal use. Similar to the main effect of green tea use on lung cancer, there was no indication of effect modification between strata of lifetime smoky coal use (Table 2). However, in an analysis stratified by green tea use (drinkers versus non-drinkers) (Table 2), an association between smoky coal exposure and lung cancer was evident in both strata with smoky coal having a greater effect on the risk of lung cancer among those who never drank green tea, although the *p* for interaction was not significant (*p* = 0.16).

Protective effects for green tea consumption were observed among individuals with susceptibility genotypes in *OGG1* and *GSTM1*, but not with *AKR1C3* (Table 3). A 72% reduction occurred among individuals with the *OGG1* Cys^{326} allele who drink green tea daily. Similarly, among *GSTM1* null homozygotes who drink green tea daily, lung cancer risk was reduced 64%, although the confidence interval included the null. Green tea consumption had little effect on lung cancer odds among *GSTM1* present or among *OGG1* Ser^{326} homozygotes. Further testing for interactions among green tea consumption, smoky coal use,

Table 2
Green tea consumption and lung cancer risk by smoky coal exposure, Xuan Wei, China

	Smoky coal < 130 tonnes				Smoky coal ≥ 130 tonnes		
	Cases	Controls	OR (95% CI)[a]		Cases	Controls	OR (95% CI)[a]
Green tea use							
Never	6	13	1.0		21	10	1.0
2–3 times per week	13	12	1.91 (0.51–7.13)		15	14	0.50 (0.17–1.47)
≥1 per day	32	47	0.96 (0.25–3.74)		35	25	0.73 (0.25–2.16)
p for trend			0.65				0.61
p interaction				0.52			
	Green tea non-drinkers				Green tea drinkers		
Smoky coal use							
<130 tonnes	6	13	1.0		45	59	1.0
≥130 tonnes	21	10	4.93 (1.27–19.13)		50	39	1.88 (1.01–3.48)
p interaction				0.16			

[a] Adjusted for age and gender.

Table 3
Green tea consumption and lung cancer risk by *OGG1*, *GSTM1*, and *AKR1C3* polymorphisms; Xuan Wei, China

Green tea use	*OGG1* Ser/Ser			*OGG1* Ser/Cys + Cys/Cys			*GSTM1* carriers			*GSTM1* null			*AKR1C3* His/His + His/Gln			*AKR1C3* Gln/Gln		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
Never	7	15	1.0	19	6	1.0	6	14	1.0	21	9	1.0	5	7	1.0	21	14	1.0
2–3 times per week	7	10	1.18 (0.28–5.04)	21	13	0.48 (0.15–1.54)	9	14	1.46 (0.40–5.35)	19	12	0.63 (0.21–1.87)	7	8	0.96 (0.19–4.85)	21	16	0.96 (0.36–2.52)
≥1 per day	23	25	1.53 (0.38–6.25)	41	39	0.28 (0.09–0.94)	25	33	1.67 (0.47–5.88)	42	39	0.36 (0.12–1.13)	10	17	0.25 (0.03–1.83)	52	49	0.83 (0.32–2.10)
p for trend			0.53			0.04			0.45			0.08			0.17			0.66
p interaction						0.02			0.06						0.90			

[a] Adjusted for age and gender.

and *OGG1* polymorphisms was statistically significant ($p = 0.009$). However, the sample size is too small to have a definitive conclusion.

Because of the gender differences in the prevalence of green tea use, we conducted further analyses examining males and females separately. There was no indication that the effect of green tea consumption among *OGG1* Cys^{326} carriers, *GSTM1* null, or *AKR1C3* Gln^{5} homozygotes differed by gender (data not shown).

4. Discussion

Overall, there was a suggestion that green tea consumption reduced the risk of lung cancer among study participants, although the confidence intervals included the null. Among a sub-population of individuals with suspected susceptibility to PAH-induced lung cancer, green tea consumption appeared to reduce the risk of lung cancer even further. Individuals with susceptible genetic polymorphisms in *OGG1* who consumed green tea daily had a reduced risk of lung cancer compared with those who never drank green tea, while among individuals with the wild genotype, green tea consumption was not associated with lung cancer risk. For *GSTM1* null homozygotes, green tea use was suggestive of a reduction in lung cancer risk.

Green tea polyphenols, the hypothesized active ingredient, have been reported to exhibit numerous chemopreventive effects in vitro and in animal bioassays. For instance, topical application of extracted green tea polyphenols decreased the incidence of skin tumors induced by topically applied PAHs (7,12-dimethylbenz[*a*]anthracene or 3-methylanthrene) to female BALB/c mice [30]. In addition, green tea polyphenols administered to female A/J mice exposed to 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) inhibited the formation of lung tumors at both the initiation and promotion stages of tumorigenesis [31]. In another experiment, green tea polyphenols prevented the formation of lipid peroxides in female SKH-1 hairless mice exposed to UVB radiation [32], suggesting that green tea polyphenols may be potent antioxidants. Paradoxically, green tea polyphenols also have been shown to inhibit in vitro growth of lung cancer cells and induce apoptosis through the production of H_2O_2, an oxidant [33,34].

While the in vitro and animal bioassays persuasively suggest that green tea consumption should reduce the risk of lung cancer, the epidemiologic evidence is mixed. Some studies have shown a decreased risk [9–11] and others no effect [12–14], and one study suggested an increased risk of lung cancer [15]. Several explanations have been offered to explain the inconsistency between the bioassays and the epidemiologic data [3,5]. First, quantification of green tea consumption in epidemiologic studies may result in exposure misclassification that would tend to obscure any association. Second, the concentrations of green tea polyphenols used in the bioassays tend to be much higher than the concentrations to which humans are exposed in their routine consumption of green tea. Third, the bioavailability of polyphenols from green tea consumption may be very limited, since they are rapidly metabolized and excreted. In addition, previous epidemiologic studies may have obscured an association because the chemopreventive effects of green tea may be limited to genetically susceptible sub-populations. In our data, a chemopreventive effect for green tea was limited to individuals with an *OGG1* Cys^{326} allele or *GSTM1* null genotype that may make them more susceptible to oxidative DNA damage than *OGG1* Ser^{326} homozygotes or *GSTM1* carriers.

Both *OGG1* and *GSTM1* may have important roles in mitigating oxidative DNA damage and ultimately carcinogenesis. *OGG1* codes for a DNA glycosylase that is involved in base excision repair of oxidative DNA damage, specifically 8-hydroxyguanine [26,27]. Further, the functional activity of the Cys^{326} polymorphism was significantly less than that of the Ser^{326} polymorphism [35,36]. Correspondingly, several epidemiologic investigations have suggested that the Cys^{326} allele is positively associated with the risk of lung cancer [37–39], although one study found no association [40]. A previous analysis from this case-control study found that the *OGG1* Cys^{326} allele was associated with an increased risk of lung cancer [29]. In that study, the odds ratio was further increased among those with the Cys^{326} allele and with heavy smoky coal exposure.

While *OGG1* repairs oxidative DNA damage, the *GSTM1* enzyme is important in quenching and detoxifying ROS and their derivatives [28]. A recent pooled analysis (12 studies) found an OR of 1.33 (95% CI = 1.03–1.67) comparing *GSTM1* null to *GSTM1* carriers among Asians [41]. Previously, we observed a two-fold increase in the OR comparing *GSTM1* null homozygotes with *GSTM1* present homozygotes and *GSTM1* heterozygotes [18]. Individuals lacking *GSTM1* may not detoxify ROS and their derivatives, thereby making them more susceptible to oxidative DNA damage. Considering that the PAHs present in smoky coal are thought to be responsible for inducing lung cancer in this population and that exposure to PAHs can induce oxidative damage [23–25], it is not surprising to observe that those individuals with deficiencies in repairing oxidative DNA damage or who lack the *GSTM1* enzyme may be at greater risk for lung cancer. Analogously, the chemopreventive effects of green tea use only may be apparent among those individuals with such deficiencies.

Given the relatively small sample size of this case-control study, cautious interpretations are necessary. A relatively small proportion of participants abstained from drinking green tea; consequently, the reference groups for the stratified analyses were small, resulting in relatively wide confidence intervals. In addition, the small sample size may have generated a false positive result by chance alone. Another potential limitation is that the quantification of green tea consumption was relatively crude and resulted in misclassification.

In conclusion, green tea consumption may be associated with a general reduction in lung cancer risk in this population. Among individuals with the *OGG1* Cys^{326} allele, green tea use was associated with a reduction in lung cancer risk. Our explanation for this finding is speculative, and however plausible it may seem that green tea may offer protection only to those who are genetically susceptible to oxidative damage from PAHs present in smoky coal, replication of these findings is needed before inferences can be made.

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